Claims 1-13 and 15-24 were examined and were rejected.

Claims 4, 8-11, 17, 20, and 24 are amended for clarity, and to more particularly point out and distinctly claim the invention. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 4, 8-11, 17, 20, and 24 is found in the claims as originally filed, and throughout the specification. Accordingly, no new matter is added by these amendments.

Claims 13, 15, and 16 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

For the Examiner's convenience, a copy of the pending claims as amended is provided in an Appendix attached hereto.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-13, and 15-24 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification allegedly does not enable a person skilled in the art to make and use the invention commensurate in scope with the claims.

Specifically, the Office Action stated that the specification does not enable a person skilled in the art to detect a bipolar mood disorder locus or polymorphism within the recited region without undue experimentation. Applicants respectfully traverse.

The cited art

The Office Action cited various publications in support of the contention that the "teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder or for detecting a bipolar (BP) susceptibility locus without undue experimentation because of the extensive amount of unpredictability in this field." Office Action, page 5. The cited art are Stine et al. ((1995) *Am. J. Hum. Genet.* 57:1384-1394; hereinafter "Stine"); McInnes et al. ((1996) *Proc. Natl. Acad. Sci.* 93:13060-13065; hereinafter "the McInnes reference"); Esterling et al. ((1997) *Molec. Psychiatry* 2:501-504; hereinafter "Esterling");

Ewald et al. ((1997) *Psychiatric Genetics* 7:1-12; hereinafter "Ewald"); Gershon et al. ((1998) *Neuropsychopharmacology* 18:233-242; hereinafter "Gershon"); and Nöthen et al. ((1999) *Molec. Psychiatry* 4:76-84; hereinafter "Nöthen").

Comments regarding the instant invention

The present invention is based on studies that differed from previous studies in several respects. These differences can account for the failure of others, and the success of the present inventors, in finding polymorphisms associated with BP. These difference include: (1) others reported **pedigree-based studies**, while the present invention relates to a **population-based study**; (2) others did not use **linkage disequilibrium analysis**; and (3) others **included irrelevant phenotypes**, while the present study **excluded irrelevant phenotypes**. These differences are described in more detail in the following paragraphs.s

(1) *While others have based their studies on unrelated families, the present inventors' data are based on population studies.*

Others have attempted to associate BP with a chromosomal locus or polymorphisms using small families or extended families. **The studies of others are pedigree-based studies**. Even if the total number of subjects analyzed was large, these subjects were typically composed of many unrelated families. **Pedigree-based studies use linkage analysis to analyze the data.** This type of analysis is **imprecise** when the genetic mode of transmission is not known, as is the case with psychiatric disorders. *This is why the results of others have been difficult to replicate and have been fraught with false positives*. Furthermore, others in the field have not pinpointed a tight interval for localization of a polymorphism.

The work of others has never been based on population studies. **The current study is very different from the others because it is a population-based study using individuals distantly related to a common ancestor from a genetically isolated founder population, and not large families. The type of analysis used in this population-based study is linkage disequilibrium analysis.** The present inventors succeeded in identifying polymorphisms that are unequivocally associated with BP because the inventors have used as their subjects **a large number of distantly related individuals** whose ancestry could be traced to a founding population.

(2) *Because the work of others was based on isolated, unrelated families, the data were not amenable to analysis using linkage disequilibrium; because the present study is a population-based study, linkage disequilibrium analysis was applied.*

Rigorous statistical analysis such as linkage disequilibrium is applicable to population studies, not to pedigree-based studies. Others used pedigree-based studies. Pedigree-based studies use **linkage analysis** to analyze the data. This type of analysis is **imprecise** when the genetic mode of transmission is not known, as is the case with psychiatric disorders. Thus, the data of others which involves small, unrelated families could not be subjected to linkage disequilibrium analysis. The present inventors were able to subject their data to **linkage disequilibrium analysis** because of the nature of the study subjects, as discussed above.

(3) *Others have included in their analyses subjects whose phenotypes do not conform to a clinical diagnosis of BP; instead, they have included subjects clinically diagnosed as having unipolar disorder.*

Others, including Stine, have included in their analysis subjects clinically diagnosed with recurrent unipolar disorder (RUP), and therefore have **included irrelevant phenotypes**. Inclusion of irrelevant phenotypes makes accurate identification of polymorphisms associated with BP that much more difficult. Applicants have applied rigorous standards to the clinical evaluation of the subjects so as to **exclude irrelevant phenotypes** in the study.

Because Applicants work is based on a completely different **study design, i.e., linkage disequilibrium analysis of a large number of distantly related individuals clinically diagnosed with BP, drawn from a genetically isolated population**, and because Applicants excluded irrelevant phenotypes from the study, Applicants succeeded where others have failed.

Applicants have identified polymorphisms in the recited region which are associated with bipolar mood disorder. The Office Action stated: "The teachings in the specification do not provide the skilled artisan with a reasonable expectation that he will identify polymorphisms that are associated with bipolar mood disorder" (Office Action, page 5), yet ***this is exactly what the Applicants have accomplished***. As the Office Action correctly noted, the specification teaches that the marker D18S59

showed the strongest evidence for linkage to bipolar disease. *D18S59 is a polymorphic marker.* An allele size of 154 base pairs at D18S59 is linked to BP. *This is a type of polymorphism.* As discussed in pages 31-32 of an article by S.J. Payne (in Laboratory Methods for the Detection of Mutations and Polymorphisms in DNA, (1997) G.R. Taylor, ed. CRC Press; a copy of page 31-32 is provided as Exhibit 1 attached hereto), microsatellite markers are highly polymorphic, often have multiple alleles, many with heterozygosity frequencies of 70% or more, and are thus highly informative for genetic analysis. Individuals with an allele size at marker D18S59 other than 154 base pairs are statistically less likely to develop BP. Applicants also found that an allele size of 271 at marker D18S476 is also associated with BP. Thus, Applicants found at least two polymorphisms in the very narrow region of chromosome 18 that are unequivocally associated with BP.

It is also important to note that *the present invention as claimed is not directed to identification of a gene associated with BP. Rather, the claimed invention is directed to methods involving analyzing a DNA sample for the presence of a DNA polymorphism associated with BP, which polymorphism occurs within the recited region on chromosome 18.* That is all that is required. Applicants have provided (1) at least two polymorphisms associated with BP that occur within the recited region of chromosome 18; and (2) ample description of how to find additional such polymorphisms. Thus, Applicants have met the statutory requirement for enablement under 35 U.S.C. §112, first paragraph.

Comments regarding McInnes, Stine, Ewald, Esterling, Gershon, and Nöthen

It should be noted that none of the cited art relates to population-based studies, as was done in the present invention. **Instead, each of the cited references describes pedigree-based studies, not population-based studies, as in the present invention.** Because the work discussed in the cited art were not population-based studies, the data were not amenable to **linkage disequilibrium analysis**, as was possible in the present invention. Thus, it is not surprising that the results reported by others have proved inconclusive. Accordingly, the cited art discussed below is not relevant in any way to an analysis of enablement of the instant invention.

The McInnes reference: The McInnes reference **analyzed extended families, and used linkage analysis.** The Office Action stated that the McInnes reference teaches that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder, and

further stated that the McInnes reference teaches that the second and third stages in their process were delineating clear candidate regions so as to identify genes associated with BP. *The present invention as claimed is not directed to genes associated with bipolar mood disorder.* Instead, the claimed invention is directed to methods involving analyzing a DNA sample for the presence of a DNA polymorphism associated with BP. Applicants note that the McInnes reference did not use linkage disequilibrium analysis of a large number of unrelated individuals, as in the present study, and thus cannot be used to show lack of enablement of the instant invention as claimed. **Thus, the McInnes reference describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.**

Stine: The Office Action stated that Stine "showed evidence of linkage between bipolar disorder and markers on the short arm of chromosome 18, i.e., 18p including marker D18S59 (table 1)." Office Action, page 3. This latter statement is inaccurate, as discussed in the response to the July 28, 1999 Office Action. A careful reading of Stine's Table 1, as well as the text of Stine, clearly show that Stine found no linkage between bipolar and D18S59. The Office Action further stated that Stine "acknowledged that the number of loci and their precise location require further study." Office Action, page 3. Stine conducted a study of 28 nuclear families. These families were unrelated to one another, and therefore the data obtained were not amenable to linkage disequilibrium analysis, as was done in the present invention. **Thus, Stine describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.** The fact that Stine found no linkage of D18S59 with BP only further emphasizes the inadequacies of the Stine study and the superior nature of the study of the present application.

Esterling: The Office Action stated that Esterling constructed a high resolution map of 18p11.2 which they state contains a potential BP susceptibility locus, and that despite having the map, no specific polymorphisms or loci have been identified as a bipolar susceptibility locus. Esterling merely describes development of a high-resolution map of the 18p11.2 region. Esterling does not describe any attempts whatsoever to identify a polymorphism associated with BP in the region studied. Accordingly, the relevance of Esterling's disclosure to the question of enablement of the instant specification is unclear.

Ewald: The Office Action stated that Ewald teaches that while chromosome 18 is one of the most promising chromosomes to contain a bipolar susceptibility locus, the research is still considered a search for susceptiblity genes. First, Ewald reports on the results of a study of Danish families. As with

the Stine study, these studies were conducted with isolated, unrelated families. Thus, the data were not amenable to the rigorous analysis to which the data presented in the instant application were subjected. **Accordingly, Ewald describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.** Second, *the present invention as claimed is not directed to specific genes associated with bipolar mood disorder*. Instead, all that is required in the present invention as claimed is that one be able to analyze a sample of DNA for a polymorphism associated with BP, said polymorphism being in the recited region of chromosome 18.

Gershon: The Office Action stated that Gershon teaches that scientists are yet a long way from demonstrating disease mutations in BP. Gershon here is referring to the identification of genes associated with BP. The title of Gershon's publication is "Closing in on genes for manic-depressive illness and schizophrenia." *The present invention as claimed is not directed to specific genes associated with bipolar mood disorder*. Instead, all that is required in the present invention as claimed is that one be able to analyze a sample of DNA for a polymorphism associated with BP, said polymorphism being in the recited region of chromosome 18.

Gershon summarizes several of the reports in the literature attempting to identify linkage of a chromosomal region with BP. Gershon, Table 1, page 236. Gershon states "*there is an uncomfortable number of nonreplications for the findings in Table 1*." Gershon, page 236, column 1, first sentence of second full paragraph, emphasis added. Gershon further remarks, with regard to the studies cited in Table 1: "*There is very little statistical power to detect this sort of linkage in the sample sizes commonly used*." Gershon, page 236, column 2, lines 7-8 of first incomplete paragraph, emphasis added. Thus, Gershon recognized the shortcomings of the work of others **and, as discussed in detail above, others have described pedigree-based studies, not a population-based study, and linkage disequilibrium analysis was not used.** Therefore, Gershon's critique cannot be fairly cited as a critique of the work of the claimed invention. The teaching of Gershon cannot be relied upon to support a conclusion of non-enablement of the instant invention as claimed.

Nöthen: The Office Action stated that Nöthen concluded as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may exist on chromosome 18, but does not provide a reasonable expectation as of yet that polymorphism in the region of 18p is associated with a bipolar susceptibility locus or what that locus will be. Nöthen reports on results of a study of 57 unrelated German families, and stated that the analysis revealed no robust evidence for linkage. This

finding is not surprising in view of the foregoing discussion of the requirements for unequivocal linkage. As with the findings reported in Stine, Ewald, Esterling, and Gershon, the data in Nöthen were not amenable to linkage disequilibrium analysis. **Nöthen describes a pedigree-based study, not a population-based study, and linkage disequilibrium analysis was not used.**

In conclusion, the work described in Stine, Ewald, Esterling, Gershon, and Nöthen suffer from at least two drawbacks, as compared to the work of Applicants. These other studies used **pedigree-based studies,** sample sizes that were too small, and involved unrelated families. Because of the small sample sizes and lack of relatedness, the data were not amenable to rigorous statistical analysis. Thus, the failure of others in the field is merely a reflection of the fact that the systems analyzed by others are inadequate to support detection of DNA polymorphisms associated with susceptibility to developing BP. Indeed, as stated in the instant specification, "earlier studies used largely uninformative markers and did not use stringent criteria for identifying affected individuals." Specification, page 4, lines 4-5.

Applicants submit that the rejection of claims 1-13, and 15-24 under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §102(a)

Claims 15 and 16 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Stine.

Without conceding as to the correctness of this rejection, claims 15 and 16 are canceled without prejudice to renewal, thereby rendering this rejection moot.

III. CONCLUSION

Applicants submit that all claims are now in condition for allowance, which action is respectfully requested. If the Examiner finds that a telephone conference would expedite prosecution, she is invited to telephone the undersigned at the number provided below.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number 6510-142 CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 17, 2000

By: 

Paula A. Borden
Registration No. 42,344

Enclosures: Exhibit 1: pp 31-32 of Payne article

BOZICEVIC, FIELD & FRANCIS LLP
285 Hamilton Avenue, Suite 200
Palo Alto, California 94301
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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